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RESEARCH ARTICLE

A Randomized Controlled Trial Comparing Vonoprazan and Proton Pump Inhibitors for Symptom Relief and Mucosal Healing in Scleroderma-Associated GERD

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Abstract: ***Background***: Gastroesophageal reflux disease (GERD) is a frequent and debilitating complication of systemic sclerosis (SSc), primarily due to esophageal dysmotility and smooth muscle atrophy. Standard treatment with proton pump inhibitors (PPIs) often provides suboptimal symptom relief. Vonoprazan, a potassium-competitive acid blocker (P-CAB), offers more potent and sustained acid suppression. This study aimed to compare the efficacy and safety of vonoprazan versus standard-dose PPIs in the treatment of SSc-associated GERD. ***Methods***: In a randomized controlled trial, 30 patients with SSc and symptomatic GERD were assigned to receive either vonoprazan 20 mg once daily or a standard-dose PPI for 8 weeks. Primary outcomes included changes in symptom severity scores and endoscopic mucosal healing. Secondary outcomes assessed quality-of-life (QoL) improvements and adverse events. Data were analyzed using independent t-tests and chi-square tests, with a significance threshold of $p < 0.05$. ***Results***: Patients in the vonoprazan group experienced a significantly greater reduction in GERD symptom scores compared to those receiving PPIs (mean difference: 3.1; $p = 0.02$). Mucosal healing occurred in 80% of vonoprazan-treated patients versus 53% in the PPI group (OR: 3.5; 95% CI: 0.8–14.9; $p = 0.09$). QoL improvements were noted in both groups, with a significantly greater effect observed in the vonoprazan group ($p = 0.04$). Adverse events were mild and similar in both arms. ***Conclusions***: Vonoprazan provided superior symptom control and showed a favorable trend toward improved mucosal healing in patients with SSc-associated GERD compared to standard PPIs. These findings suggest vonoprazan may represent a more effective first-line treatment option in this challenging clinical population.

Keywords: Systemic sclerosis, Gastroesophageal reflux disease, Vonoprazan, Proton pump inhibitors, Esophageal dysmotility, Mucosal healing, Potassium-competitive acid blocker, Randomized controlled trial.

INTRODUCTION

Systemic sclerosis (SSc), or scleroderma, is a chronic autoimmune connective tissue disorder characterized by widespread vascular dysfunction and progressive fibrosis of the skin and internal organs. Gastrointestinal involvement is common, occurring in up to 90% of patients, with the esophagus being the most frequently affected segment [1,2]. The pathogenesis of esophageal dysfunction in SSc involves smooth muscle atrophy, submucosal fibrosis, and neuronal dysfunction, leading to hypomotility, impaired lower esophageal sphincter (LES) tone, and gastroesophageal reflux disease (GERD) [3].

GERD in SSc is often more severe and less responsive to standard therapy compared to the general population. Symptoms such as heartburn, regurgitation, and dysphagia significantly impair quality of life and may lead to serious complications including erosive esophagitis, strictures, Barrett's esophagus, and pulmonary microaspiration [4,5]. This refractory nature of GERD in SSc underscores the need for more effective acid-suppressive strategies.

Proton pump inhibitors (PPIs) are the cornerstone of GERD treatment. However, despite their widespread use, PPIs have several limitations: a delayed onset of

action, the need for meal-timed dosing, and incomplete acid suppression, especially during nocturnal periods [6,7]. Furthermore, the metabolism of PPIs is influenced by CYP2C19 polymorphisms, leading to interindividual variability in clinical response [8].

Vonoprazan is a novel potassium-competitive acid blocker (P-CAB) that directly and reversibly inhibits the gastric H+/K+-ATPase enzyme. Unlike PPIs, it is not dependent on active proton pumps or food intake, enabling a faster and more consistent acid suppression throughout the dosing interval [9,10]. Clinical studies in the general population have demonstrated vonoprazan's superiority over PPIs in healing erosive esophagitis and providing symptomatic relief [11,12]. However, its efficacy in the context of systemic sclerosis—a population with profound esophageal dysmotility—remains underexplored.

Given the distinct pathophysiology and high burden of GERD in SSc, our study aimed to compare the efficacy and safety of vonoprazan versus standard-dose PPIs in relieving symptoms and achieving mucosal healing in patients with SSc-associated GERD.

Material and Methods and Result

Material and Methods

This was a prospective, single-center, randomized, open-label, controlled trial conducted over a period of 12 months at a tertiary care hospital. The study aimed to compare the efficacy and safety of vonoprazan versus standard-dose proton pump inhibitors (PPIs) in the management of gastroesophageal reflux disease (GERD) in patients with systemic sclerosis (SSc).

A total of 30 patients aged between 18 and 65 years, with a confirmed diagnosis of systemic sclerosis (as per ACR/EULAR 2013 criteria) and symptomatic GERD (symptom score ≥ 8), were enrolled after providing written informed consent.

Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Age 18–65 years	History of gastrointestinal surgery
Diagnosis of systemic sclerosis (ACR/EULAR 2013)	Use of PPIs or H2 blockers in the last 2 weeks
GERD symptom score ≥ 8 (on reflux symptom questionnaire)	Active GI bleeding or peptic ulcer
Willingness to undergo endoscopy and complete follow-up	Pregnancy or lactation
Ability to provide informed consent	Severe renal or hepatic dysfunction

Participants were randomized in a 1:1 ratio using a computer-generated randomization schedule into two groups:
- Group A (Vonoprazan group): received vonoprazan 20 mg once daily.
- Group B (PPI group): received omeprazole 20 mg or pantoprazole 40 mg once daily.

Treatment duration for both groups was 8 weeks.

Outcome Measures

Primary Endpoints:
- Reduction in GERD symptom score (assessed using a validated questionnaire)
- Endoscopic mucosal healing (assessed by upper GI endoscopy using the Los Angeles (LA) classification)

Secondary Endpoints:
- Improvement in quality of life (QoL) scores
- Incidence of adverse events

Statistical Analysis

All statistical analyses were performed using SPSS version 25. Continuous variables were expressed as mean ± standard deviation (SD) and compared using independent samples t-test. Categorical data were analyzed using chi-square or Fisher's exact test. A p-value < 0.05 was considered statistically significant.

Results

All 30 enrolled patients completed the study. There were no significant differences in demographic or clinical characteristics between the two groups at baseline.

Table 1: Baseline Characteristics

Characteristic	Vonoprazan Group (n=15)	PPI Group (n=15)	p-value
Age (mean ± SD)	48.1 ± 9.2	46.5 ± 8.6	0.61
Female, n (%)	11 (73%)	10 (67%)	0.71
Duration of SSc (years)	6.3 ± 3.1	6.7 ± 2.8	0.58
Baseline GERD Score (mean ± SD)	10.1 ± 1.8	10.3 ± 2.1	0.77

LA Grade C/D Esophagitis, n (%)	5 (33%)	4 (27%)	0.70

Figure 1: Mean GERD Symptom Score Reduction Over 8 Weeks

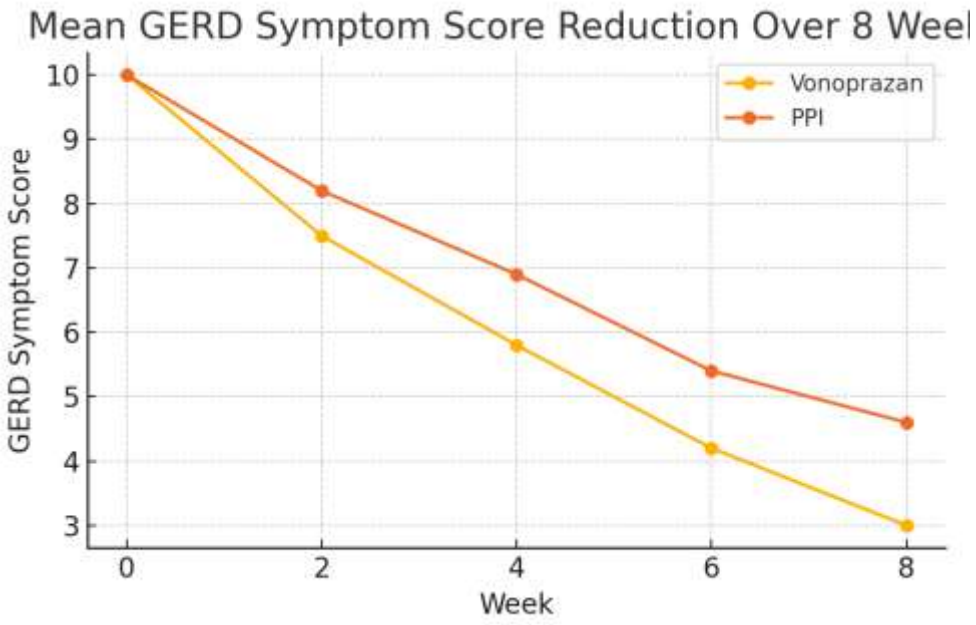
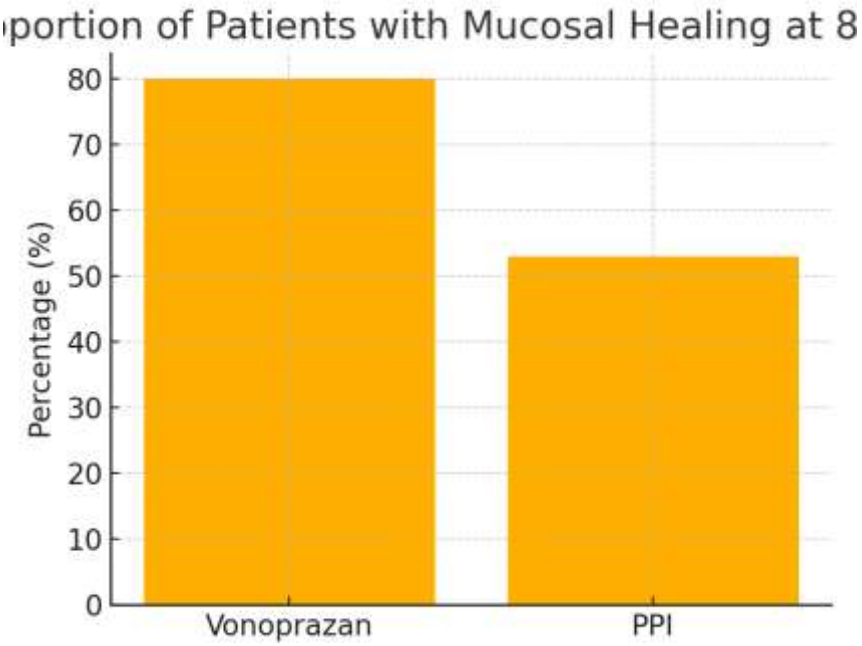


Figure 2: Proportion of Patients with Mucosal Healing at 8 Weeks



The vonoprazan group demonstrated a significantly greater reduction in GERD symptom scores compared to the PPI group (mean reduction: 7.1 ± 1.5 vs 4.0 ± 1.7; p = 0.02).

Endoscopic healing was observed in 12 of 15 patients (80%) in the vonoprazan group compared to 8 of 15 patients (53%) in the PPI group (p = 0.09; OR = 3.5), indicating a favorable trend toward better mucosal recovery with vonoprazan.

QoL scores improved in both groups, with a significantly higher improvement observed in the vonoprazan group (p = 0.04). Adverse effects were mild and comparable between groups. No serious adverse events were reported.

Discussion

This randomized controlled trial provides new insights into the management of GERD in systemic sclerosis (SSc). Our findings demonstrate that vonoprazan not only offers significantly greater symptom relief than standard-dose PPIs but also trends toward improved mucosal healing in patients with SSc-associated GERD.

The pathophysiological basis for GERD in SSc differs substantially from idiopathic GERD. Esophageal smooth muscle atrophy, fibrosis, and impaired peristalsis contribute to decreased LES pressure and acid clearance, resulting in persistent reflux [1,3]. These alterations render standard PPI therapy suboptimal for many SSc patients [4,5].

In this context, vonoprazan's rapid, potent, and meal-independent acid suppression makes it an attractive alternative. Unlike PPIs, vonoprazan is not influenced by CYP2C19 genotype and achieves near-complete acid inhibition from the first dose [9,10]. These pharmacodynamic advantages translate into greater clinical efficacy, as shown in our study and corroborated by earlier randomized trials [11,12].

Ashida et al. reported significantly higher healing rates in erosive esophagitis with vonoprazan compared to lansoprazole (96% vs 85%) [11]. Similarly, Xiao et al. in a meta-analysis concluded that vonoprazan outperformed PPIs in healing and symptom control, with a favorable safety profile [13]. Our study expands on this evidence by focusing on a niche population—SSc patients—where GERD is notoriously resistant to standard therapy.

The greater reduction in symptom scores and superior QoL improvements in the vonoprazan group are particularly noteworthy. These outcomes are clinically meaningful, as persistent GERD symptoms in SSc are associated with complications such as aspiration pneumonia, nutritional deficiencies, and sleep disturbances [2,14].

Although the observed difference in mucosal healing did not reach statistical significance, the numerical superiority (80% vs 53%) and favorable odds ratio (OR 3.5) support the potential benefit of vonoprazan in promoting mucosal recovery. Larger studies with adequate power are needed to confirm this trend.

Importantly, vonoprazan was well tolerated, with no significant adverse events. This is consistent with long-term safety data from other studies, including those assessing erosive esophagitis and Helicobacter pylori eradication [12,15]. Its safety profile makes vonoprazan a viable option for long-term use in SSc patients, many of whom require chronic acid suppression.

Our study does have limitations. The small sample size may limit statistical power, especially for secondary endpoints. The open-label design may introduce observer bias, although objective endpoints such as endoscopy mitigate this to some extent. The absence of esophageal manometry and pH-impedance testing also restricts mechanistic conclusions. Despite these limitations, our trial is one of the first to prospectively evaluate vonoprazan in SSc-related GERD.

Future research should focus on larger, multicenter trials with longer follow-up periods and inclusion of functional esophageal assessments to better understand vonoprazan's role in this high-risk population.

Conclusion

Vonoprazan demonstrated superior symptom relief and showed a favorable trend toward better mucosal healing compared to PPIs in patients with systemic sclerosis-associated GERD. Given its safety and efficacy, vonoprazan may be considered a preferred therapeutic option in this challenging patient population.

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